



US006548494B1

(12) **United States Patent**
Webber et al.

(10) **Patent No.:** US 6,548,494 B1
(45) **Date of Patent:** Apr. 15, 2003

(54) **TRICYCLIC INHIBITORS OF POLY(ADP-RIBOSE) POLYMERASES**

(75) **Inventors:** Stephen Evan Webber, San Diego, CA (US); Donald James Skaltitzky, San Diego, CA (US); Jayashree Girish Tikhe, San Diego, CA (US); Robert Arnold Kumpf, Encinitas, CA (US); Joseph Timothy Marakovits, Encinitas, CA (US); Brian Walter Eastman, San Diego, CA (US)

(73) **Assignee:** Agouron Pharmaceuticals, Inc., San Diego, CA (US)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** 09/653,184

(22) **Filed:** Aug. 31, 2000

Related U.S. Application Data

(60) Provisional application No. 60/152,142, filed on Aug. 31, 1999.

(51) **Int. Cl.⁷** C07D 487/06; A61K 31/5517; A61P 35/00

(52) **U.S. Cl.** 514/220; 540/496; 540/499

(58) **Field of Search** 540/496, 499; 514/220

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WO	WO 95/26186	10/1995
WO	WO 97/04771	2/1997
WO	WO 97/19934	6/1997
WO	WO 98/33802	8/1998
WO	WO 98/51307	11/1998
WO	WO 98/51308	11/1998
WO	WO 99/11622	3/1999
WO	WO 99/11623	3/1999

WO	WO 99/11624	3/1999
WO	WO 99/11628	3/1999
WO	WO 99/11644	3/1999
WO	WO 99/11645	3/1999
WO	WO 99/11649	3/1999
WO	WO 99/59973	11/1999
WO	WO 99/59975	11/1999

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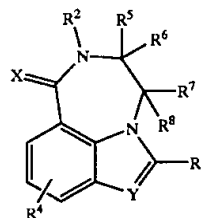
(List continued on next page.)

Primary Examiner—Bruck Kifle

(74) *Attorney, Agent, or Firm*—Karl Neidert; Bryan C. Zielinski; Peter Richardson

(57) ABSTRACT

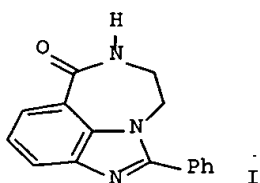
Compounds of the formula shown below are poly(ADP-ribosyl)transferase inhibitors:



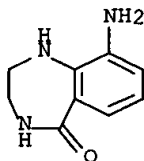
Such compounds are useful as therapeutics in treating cancers and in ameliorating the effects of stroke, head trauma, and neurodegenerative disease.

13 Claims, No Drawings

L4 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 2002:954525 CAPLUS
 DN 138:170205
 TI Tricyclic Benzimidazoles as Potent Poly(ADP-ribose) Polymerase-1 Inhibitors
 AU Skaltitzky, Donald J.; Marakovits, Joseph T.; Maegley, Karen A.; Ekker, Anne; Yu, Xiao-Hong; Hostomsky, Zdenek; Webber, Stephen E.; Eastman, Brian W.; Almasy, Robert; Li, Jianke; Curtin, Nicola J.; Newell, David R.; Calvert, A. Hilary; Griffin, Roger J.; Golding, Bernard T.
 CS Pfizer Global R&D, La Jolla/Agouron Pharmaceuticals Inc., San Diego, CA, 92121, USA
 SO Journal of Medicinal Chemistry (2003), 46(2), 210-213
 CODEN: JMCMAR; ISSN: 0022-2623
 PB American Chemical Society
 DT Journal
 LA English
 OS CASREACT 138:170205
 GI



AB Novel tricyclic benzimidazole carboxamide poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors, e.g., I, have been synthesized. Several compds. were found to be powerful chemopotentiators of temozolomide and topotecan in both A549 and LoVo cell lines. In vitro inhibition of PARP-1 was confirmed by direct measurement of NAD⁺ depletion and ADP-ribose polymer formation caused by chem. induced DNA damage.
 IT **328546-66-3P**
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (prepn. of intermediate aminobenzodiazepinone via cyclization of nitrobromobenzoic acid Me ester with ethylene diamine and subsequent redn.)
 RN 328546-66-3 CAPLUS
 CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



RE.CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:428911 CAPLUS
DN 137:6205

TI Preparation of benzazepinones, isoquinolinones and related compounds as inhibitors of poly(ADP-ribose) polymerase (PARP) for the prevention and/or treatment of tissue damage from cell trauma or cell death due to necrosis or apoptosis.

IN Ferraris, Dana V.; Li, Jia-He; Kalish, Vincent J.; Zhang, Jie

PA Guilford Pharmaceuticals Inc., USA

SO PCT Int. Appl., 152 pp.

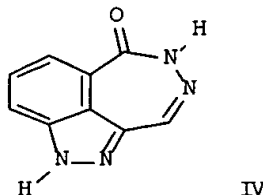
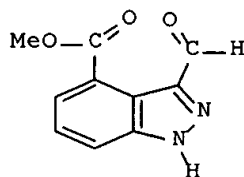
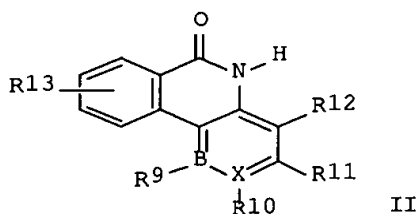
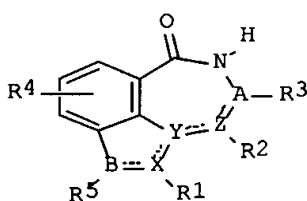
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

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PI	WO 2002044183	A2	20020606	WO 2001-US44815	20011130
	WO 2002044183	A3	20030522		
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	AU 2002036521	A5	20020611	AU 2002-36521	20011130
	US 2003022883	A1	20030130	US 2001-996776	20011130
	EP 1339402	A2	20030903	EP 2001-986053	20011130
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
PRAI	US 2000-250132P	P	20001201		
	US 2001-310274P	P	20010809		
	WO 2001-US44815	W	20011130		
OS	MARPAT 137:6205				
GI					



AB This invention discloses the prepn. of title compds. I and II, their pharmaceutically acceptable salts, and related compds. as inhibitors of poly(ADP-ribose) polymerase (PARP) [wherein: A = N, C, CH2, CH; B = C, N,

NH, S, SO, SO₂; X = C, CH, N; Y = C, N; Z = C, CH₂, N, CO; provided that at least one of X, Y, or Z is N; R₁, R₂, R₃, R₅ when present are optionally or independently = H, OH, :O, (un)substituted alkyl, alkenyl, alkynyl, alkoxy, carboxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, halogen, amine, COR₈ (R₈ = H, OH, (un)substituted alkyl, alkenyl, alkynyl, alkoxy, carboxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl), OR₆, NR₆R₇ (R₆, R₇ independently = H, (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl); R₁, R₂, R₃, R₅ optionally

form ring through a straight or branched C₁-4alkyl which may addnl. contain 1-2 double or triple bonds; R₄ = 1-3 of H, halo, or alkyl; with proviso that when A, X, or Z = C, then R₁, R₂, R₃ when present may also independently = halogen, CN, O; R₉, R₁₀, R₁₁, R₁₂ optionally or independently = H, halogen, amino, OH, halo-amine, O-alkyl, O-aryl, (un)substituted alkyl, alkenyl, alkynyl, alkoxy, carboxy, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, COR₈; R₁₃ = 1-3 of H, halogen, alkoxy, alkyl]. For example, cyclocondensation of formylindazole III (prepd. from

Me indole-4-carboxylate and NaNO₂/AcOH), with hydrazine provided claimed benzoazulenone IV as a white solid. Benzoazulenone IV inhibited human recombinant PARP at an IC₅₀ of 0.018 .mu.M. PARP IC₅₀ inhibition studies

for an addnl. 156 examples are provided, ranging in values from 0.01 to 20

.mu.M. Biol. data are provided for the in vivo treatment of focal cerebral ischemia and gout via PARP inhibition with selected compds. II. The present invention is believed to protect cells, tissue and organs against the ill-effects of reactive free radicals and nitric oxide through

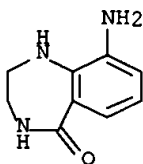
inhibition of PARP activity.

IT **328546-66-3P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT(Reactant or reagent)(intermediate; prepn. of benzazepinones, isoquinolinones and related compds. as inhibitors of poly(ADP-ribose) polymerase (PARP))

RN 328546-66-3 CAPLUS

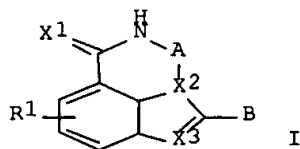
CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L4 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 2001:225212 CAPLUS
 DN 134:266331
 TI Preparation of 2-phenyl-5,6-dihydro-imidazo[4,5,1-jk][1,4]benzodiazepin-
 7(4H)-ones as poly(ADP ribose) polymerase inhibitors.
 IN Lubisch, Wilfried; Kock, Michael; Hoeger, Thomas; Grandel, Roland;
 Mueller, Reinhold; Schult, Sabine
 PA BASF A.-G., Germany
 SO Ger. Offen., 12 pp.
 CODEN: GWXXBX
 DT Patent
 LA German
 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 19946289	A1	20010329	DE 1999-19946289	19990928
	WO 2001023386	A2	20010405	WO 2000-EP9023	20000915
	WO 2001023386	A3	20020510		
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	WO 2001023390	A3	20011227		
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	EP 1183259	A2	20020306	EP 2000-974379	20000915
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	EP 1222191	A2	20020717	EP 2000-966022	20000915
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	NO 2001002567	A	20010625	NO 2001-2567	20010525
	BG 105650	A	20020228	BG 2001-105650	20010626
	BG 106444	A	20020930	BG 2002-106444	20020226
	NO 2002001379	A	20020320	NO 2002-1379	20020320
PRAI	DE 1999-19946289	A	19990928		
	DE 2000-10039610	A	20000809		
	WO 2000-EP9023	W	20000915		
	WO 2000-EP9024	W	20000915		

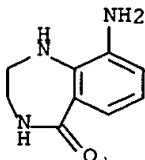
OS MARPAT 134:266331
GI



AB Title compds. [I; A = (substituted) C1-3 alkylene; X1 = S, O, NE; X2 = N, (substituted) C; X3 = N, CR2; R2 = H, alkyl, alkylphenyl, Ph; R1 = H, halo, OH, NO2, CF3, cyano, alkyl, alkoxy, etc.; B = (unsatd.) (O-, N-, S-interrupted) (substituted) mono-, bi-, tricyclic] were prepd. as poly(ADP ribose) polymerase inhibitors (no data). Thus, Me 2-chloro-3-nitrobenzoate was heated with K2CO3 and H2NCH2CH2NH2 in DMF for 3 at 120.degree. to give 9-nitro-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one, which was hydrogenated using Pd/C in EtOH to give 9-amino-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one. The latter in MeOH contg. HOAc was treated dropwise with 4-(4-methylpiperazin-1-yl)benzaldehyde in MeOH followed by 1 h stirring at room temp.; Cu(OAc)2, Na2S, and HCl in H2O were added followed by 30 min reflux to give 2-[4-(4-methylpiperazin-1-yl)phenyl]-5,6-dihydro-imidazo[4,5,1-jk][1,4]benzodiazepin-7(4H)-one.

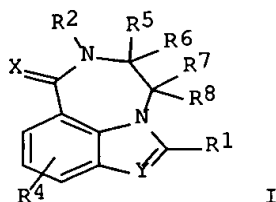
IT **328546-66-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (prepn. of phenyldihydroimidazobenzodiazepinones as PARP inhibitors)

RN 328546-66-3 CAPLUS
CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



L4 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 2001:167995 CAPLUS
 DN 134:207833
 TI Preparation of tricyclic inhibitors of poly(ADP-ribose) polymerases
 IN Webber, Stephen Evan; Skaltitzky, Donald James; Tikhe, Jayashree Girish;
 Kumpf, Robert Arnold; Marakovits, Joseph Timothy; Eastman, Walter Brian
 PA Agouron Pharmaceuticals, Inc., USA; Cancer Research Campaign Technology
 Limited
 SO PCT Int. Appl., 236 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001016136	A2	20010308	WO 2000-US23882	20000831
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	EE 200200100	A	20030616	EE 2002-100	20000831
	NO 2002000421	A	20020425	NO 2002-421	20020128
	BG 106562	A	20030331	BG 2002-106562	20020329
PRAI	US 1999-152142P	P	19990831		
	WO 2000-US23882	W	20000831		
OS	MARPAT 134:207833				
GI					



AB The title compds. [I; X = O, S; Y = N, CR3 (wherein R3 = halo, CN, alkyl, etc.); R1 = H, halo, CN, etc.; R2 = H, alkyl; R4 = H, halo, alkyl; R5-R8 =

H, alkyl, alkenyl, aryl, etc.] which are poly(ADP-ribosyl)transferase inhibitors, and are useful in treating cancers and in ameliorating the effects of stroke, head trauma, and neurodegenerative disease, were prepd.

E.g., a multi-step synthesis of 1-phenyl-8,9-dihydro-7H-2,7,9a-triaza-benzo[cd]azulen-6-one [I; Y = N; X = O; R1 = Ph; R2, R4-R8 = H] was given.

Biol. data for compds. I were presented.

IT 328546-66-3P 328546-75-4P 328546-88-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);

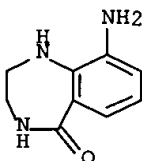
RACT

(Reactant or reagent)

(prepn. of tricyclic inhibitors of poly(ADP-ribose) polymerases)

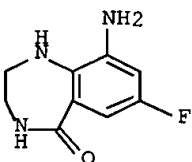
RN 328546-66-3 CAPLUS

CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



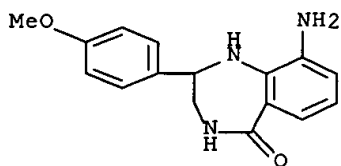
RN 328546-75-4 CAPLUS

CN 5H-1,4-Benzodiazepin-5-one, 9-amino-7-fluoro-1,2,3,4-tetrahydro- (9CI) (CA INDEX NAME)



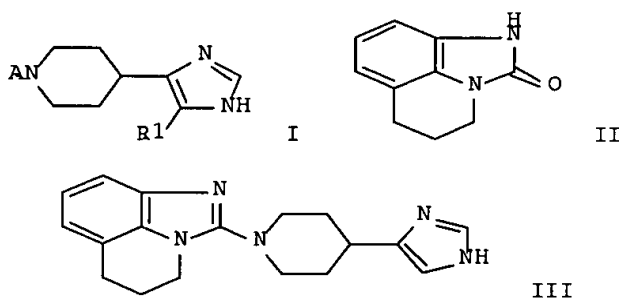
RN 328546-88-9 CAPLUS

CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro-2-(4-methoxyphenyl)- (9CI) (CA INDEX NAME)



L4 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 1995:557370 CAPLUS
 DN 122:290862
 TI Derivatives of imidazol-4-ylpiperidine with 5-HT3 and 5-HT4 activity,
 their preparation, and their use in therapy.
 IN Jegham, Samir; Defosse, Gerard; Purcell, Thomas Andrew; Even, Luc
 PA Synthelabo S. A., Fr.
 SO Eur. Pat. Appl., 17 pp.
 CODEN: EPXXDW
 DT Patent
 LA French
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 646583	A1	19950405	EP 1994-402114	19940923
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT,				
SE					
	FR 2710915	A1	19950414	FR 1993-11771	19931004
	FR 2710915	B1	19951124		
	CA 2133491	AA	19950405	CA 1994-2133491	19941003
	NO 9403682	A	19950405	NO 1994-3682	19941003
	FI 9404600	A	19950405	FI 1994-4600	19941003
	AU 9474329	A1	19950413	AU 1994-74329	19941003
	JP 07179466	A2	19950718	JP 1994-238914	19941003
	ZA 9407710	A	19950810	ZA 1994-7710	19941003
	CN 1109471	A	19951004	CN 1994-117012	19941003
	HU 71120	A2	19951128	HU 1994-2832	19941003
	US 5589476	A	19961231	US 1994-317661	19941003
PRAI	FR 1993-11771		19931004		
OS	CASREACT 122:290862; MARPAT 122:290862				
GI					



AB Title compds. I [R1 = H, straight or branched C1-6 alkyl; A = 9 specific
 tricyclic heterocyclic radicals with an optional phenylmethyl
 substituent]
 and their pharmaceutical salts are claimed. The compds. are ligands of
 5-HT3 and 5-HT4 receptors, and have a variety of potential uses
 involving
 CNS and cardiovascular activities. For example, redn. of 8-
 quinolinamine

with Na in EtOH gave the 1,2,3,4-tetrahydro deriv., which was cyclized with urea to give dihydroimidazoquinolinone II. Treatment of II with POCl₃ converted the carbonyl to the corresponding unsatd. chloride, which

reacted with 4-(1H-imidazol-4-yl)piperidine in isoamyl alc. at 120.degree.

to give title compd. III. The IC₅₀ values of more active I for inhibition

of [3H]-quipazine binding to rat cerebral 5-HT₃ receptors were 0.01-10 nM.

I also had IC₅₀ of 0.02-2 .mu.M for inhibition of specific binding of [3H]-GR118808 to guinea pig 5-HT₄ receptors.

IT **126234-17-1P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);

RACT

(Reactant or reagent)

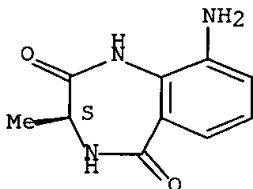
(intermediate; prepn. of imidazolylpiperidine derivs. as 5-HT₃ and 5-HT₄ receptor ligands)

RN 126234-17-1 CAPLUS

CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)- (9CI)

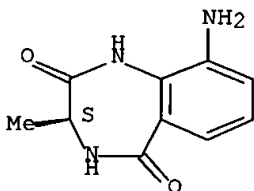
(CA INDEX NAME)

Absolute stereochemistry.

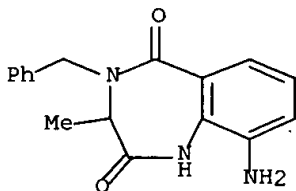


L4 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 1995:502782 CAPLUS
 DN 123:112027
 TI Synthesis of racemic and enantiomeric (S)-(+)-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one derivatives
 AU Pfaendler, Hans Rudolf; Weisner, Frank
 CS Inst. Organic Chem., Univ. Munich, Munich, D-80333, Germany
 SO Heterocycles (1995), 40(2), 717-27
 CODEN: HTCYAM; ISSN: 0385-5414
 PB Japan Institute of Heterocyclic Chemistry
 DT Journal
 LA English
 OS CASREACT 123:112027
 AB Racemic and enantiomeric (S)-(+)-4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one derivs. were prepd. using free amino acids and 3-nitroisatoic anhydride. Simultaneous redn. of two amide functions was efficiently achieved using diborane.
 IT **126234-17-1P 166044-61-7P**
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
 RACT
 (Reactant or reagent)
 (synthesis of racemic and enantiomeric tetrahydromethylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one derivs.)
 RN 126234-17-1 CAPLUS
 CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)-(9CI)
 (CA INDEX NAME)

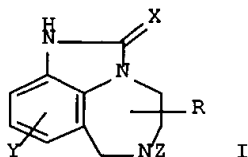
Absolute stereochemistry.



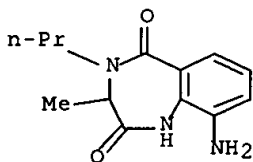
RN 166044-61-7 CAPLUS
 CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-4-(phenylmethyl)- (9CI) (CA INDEX NAME)



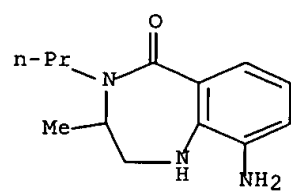
L4 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 1995:380741 CAPLUS
 DN 122:290829
 TI Synthesis and Anti-HIV-1 Activity of 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) Derivatives.
 3
 AU Breslin, Henry J.; Kukla, Michael J.; Ludovici, Donald W.; Mohrbacher, Richard; Ho, Winston; Miranda, Milton; Rodgers, James D.; Hitchens, T. Kevin; Leo, Gregory; et al.
 CS Janssen Research Foundation, Spring House, PA, 19477, USA
 SO Journal of Medicinal Chemistry (1995), 38(5), 771-93
 CODEN: JMCMAR; ISSN: 0022-2623
 PB American Chemical Society
 DT Journal
 LA English
 GI



AB 4,5,6,7-Tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-ones (TIBO) (I, R = H, 5-Et, 7-Ph, etc.; X = S, O; Y = 8-Cl, 9-Cl; Z = H, 3,3-dimethylallyl, Pr, etc.) have been shown to significantly inhibit HIV-1 replication in vitro by interfering with the virus's reverse transcriptase enzyme. We describe our synthetic endeavors around 4, 5, and 7 mono- and disubstitutions of I and discuss HIV-1 inhibitory structure-activity relationships. On the basis of inhibition of HIV-1 replication in MT-4 cells, we found that 5-mono-Me-substituted analogs and 7-mono-Me-substituted analogs of I were comparable as being consistently the most active compds. Although generally less active, the 4,5,7-unsubstituted, 4-mono-substituted, cis- and trans-5,7-di-Me-substituted, and cis-4,5-di-Me-substituted analogs of I also exhibited significant activity. The remaining trans-4,5-di-Me-substituted, cis- and trans-4,7-di-Me-substituted, and all 4,5-, 5,6-, 6,7-, and 7,8-fused disubstituted analogs of I possessed no noticeable desired activity.
 IT **131645-75-5P 162931-22-8P**
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (synthesis and anti-HIV-1 activity of imidazobenzodiazepinones)
 RN 131645-75-5 CAPLUS
 CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-4-propyl-(9CI) (CA INDEX NAME)



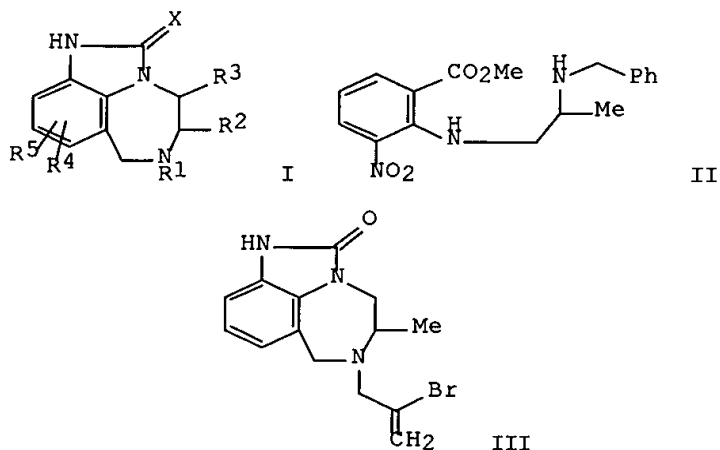
RN 162931-22-8 CAPLUS
 CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro-3-methyl-4-propyl-(9CI) (CA INDEX NAME)



L4 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 1992:235663 CAPLUS
 DN 116:235663
 TI Preparation of antiviral tetrahydroimidazo[1,4]benzodiazepin-2-(thio)ones
 IN Kukla, Michael Joseph; Breslin, Henry Joseph; Raeymaekers, Alfons Herman
 Margaretha; Van Gelder, Josephus Ludovicus Hubertus; Janssen, Paul
 Adriaan
 Jan
 PA Janssen Pharmaceutica N. V., Belg.
 SO PCT Int. Appl., 48 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9200979	A1	19920123	WO 1991-EP1224	19910628
	W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, PL, RO, SD, SU				
	RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG				
	CA 2086547	AA	19920107	CA 1991-2086547	19910628
	AU 9180683	A1	19920204	AU 1991-80683	19910628
	AU 644192	B2	19931202		
	EP 538297	A1	19930428	EP 1991-912145	19910628
	EP 538297	B1	20010919		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05508632	T2	19931202	JP 1991-511094	19910628
	HU 68382	A2	19950628	HU 1993-11	19910628
	PL 168320	B1	19960229	PL 1991-297379	19910628
	PL 169662	B1	19960830	PL 1991-309617	19910628
	PL 169613	B1	19960830	PL 1991-309618	19910628
	AT 205848	E	20011015	AT 1991-912145	19910628
	ES 2164044	T3	20020216	ES 1991-912145	19910628
	CZ 279900	B6	19950816	CZ 1991-2065	19910704
	IL 98726	A1	19960131	IL 1991-98726	19910704
	SK 278442	B6	19970507	SK 1991-2065	19910704
	ZA 9105239	A	19930331	ZA 1991-5239	19910705
	CN 1057840	A	19920115	CN 1991-104581	19910706
	CN 1034122	B	19970226		
	NO 9204853	A	19921215	NO 1992-4853	19921215
	US 5270464	A	19931214	US 1993-42858	19930405
	US 5371079	A	19941206	US 1993-132030	19931005
	US 6201119	B1	20010313	US 1994-304951	19941017
PRAI	US 1990-549349	A	19900706		
	GB 1988-6449	A	19880318		
	GB 1989-4108	A	19890223		
	US 1989-323585	B2	19890314		
	GB 1989-20354	A	19890908		
	US 1989-406625	B2	19890913		
	US 1989-406626	B2	19890913		
	US 1990-476926	B2	19900208		
	US 1990-549777	B2	19900709		
	US 1990-583533	B2	19900917		
	US 1991-671238	B1	19910319		
	WO 1991-EP1224	A	19910628		

US 1993-42858 A3 19930405
 US 1993-132030 A3 19931005
 OS MARPAT 116:235663
 GI



AB Title compds. [I; X = O, S; R1 = (substituted) alkenyl, cycloalkylalkyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, etc.; R2,R3 = H, alkyl; R4,R5 = H, alkyl, halo, cyano, NO₂, CF₃, OH, alkoxy, (alkyl)amino, alkylcarbonylamino, arylcarbonylamino], were prepd. Thus, diamine II [prepn. from Me 2-bromo-3-nitrobenzoate and (H₂NCH₂CHMe)NHCH₂Ph given] was sapond. with aq. NaOH in Me₂CHOH (82%) and the product was refluxed with SOCl₂ in PhMe to give 85% 2,3,4,5-tetrahydro-3-methyl-9-nitro-4-benzyl-1H-1,4-benzodiazepin-5-one. The latter was reduced with LiAlH₄ (87.6%) and the product was heated with urea at 210-220.degree. to give 11.5% imidazobenzodiazepinone deriv., which was hydrogenolyzed in HOAc over Pd/C to give 66.8% 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one. The latter was heated with Na₂CO₃, KI, and 2,3-dibromopropene in DMF to give title compd. III. I had ED₅₀'s of 0.032-0.006 .mu.g/mL against HIV-1 in MT-4 cells.

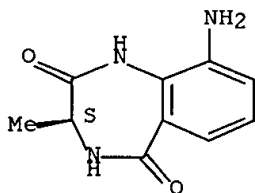
IT 126234-17-1P

RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of, as intermediate for imidazobenzodiazepinone virucide)

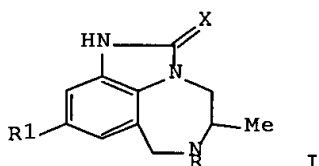
RN 126234-17-1 CAPLUS

CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)-
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.

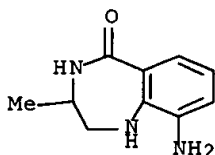


L4 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 1991:632195 CAPLUS
 DN 115:232195
 TI Synthesis and anti-HIV-1 activity of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) derivatives.
 2
 AU Kukla, Michael J.; Breslin, Henry J.; Diamond, Craig J.; Grous, Philip P.;
 Ho, Chih Y.; Miranda, Milton; Rodgers, James D.; Sherrill, Ronald G.; De Clercq, Erik; et al.
 CS Janssen Res. Found., Spring House, PA, 19477, USA
 SO Journal of Medicinal Chemistry (1991), 34(11), 3187-97
 CODEN: JMCMAR; ISSN: 0022-2623
 DT Journal
 LA English
 GI

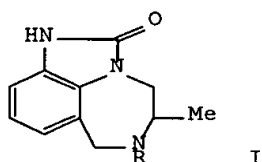


AB Potential anti-HIV-1 imidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one I (R
 =
 R1 = H, X = O) analogs with variations of the five-membered urea ring
 were
 prep'd. Although many different rings were synthesized to replace the
 cyclic urea of I, most were found to be inactive in inhibiting the
 replication of the HIV-1 virus in MT-4 cells. The exceptions were
 replacement of the urea oxygen with sulfur or selenium to give the
 corresponding thio- or selenoureas. These were found to be more active
 than the oxygen counterparts. A small series of analogs were
 synthesized
 and tested which allowed direct comparison of urea and thiourea derivs.
 Without exception, the latter were always more active than the former.
 The most active comp'd. (S)(+)-I (R = CH₂C:CEt₂, R1 = Cl, X = S) was
 found
 to inhibit the HIV-1 virus with an IC₅₀ of 0.012 .mu.M which is
 comparable
 to that of AZT.

IT **136722-94-6**
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (cyclocondensation of, with formamidine acetate)
 RN 136722-94-6 CAPLUS
 CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro-3-methyl- (9CI)
 (CA INDEX NAME)



L4 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 1991:101957 CAPLUS
 DN 114:101957
 TI Synthesis and anti-HIV-1 activity of 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one (TIBO) derivatives
 AU Kukla, Michael J.; Breslin, Henry J.; Pauwels, Rudi; Fedde, Cynthia L.; Miranda, Milton; Scott, Malcolm K.; Sherrill, Ronald G.; Raeymaekers, Alfons; Van Gelder, Jozef; et al.
 CS Janssen Res. Found., Spring House, PA, 19477, USA
 SO Journal of Medicinal Chemistry (1991), 34(2), 746-51
 CODEN: JMCMAR; ISSN: 0022-2623
 DT Journal
 LA English
 OS CASREACT 114:101957
 GI



AB Title compds. I (R = alkenyl, alkyl, heterocycloalkyl, etc.) have been synthesized and tested for their ability to inhibit the replication of the HIV-1 virus in MT-4 cells. Two synthetic methods are described, one of which allows the synthesis of single enantiomers of the final products. A structure-activity study was done within the series of compds. to det. the optimum group for the 6-position substitution and to det. whether the activity was enantiospecific at the 5-position, which was substituted with a Me group. The best analog, (S)-(+)-I (R = CH₂CH:CM₂), inhibited HIV-1 with an IC₅₀ (conc. required to protect 50% of the cells against HIV-1-induced cytopathic effects) of 4 .mu.M, which is comparable to the activity level of DDI, a 2',3'-dideoxynucleoside-type structure undergoing clin. trials as an anti AIDS therapy.

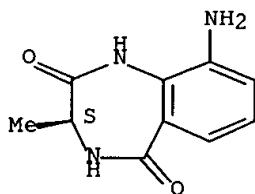
IT 126234-17-1P

RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. and sequential redn. and cyclocondensation with
 trichloromethyl chloroformate)

RN 126234-17-1 CAPLUS

CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)-
 (9CI) (CA INDEX NAME)

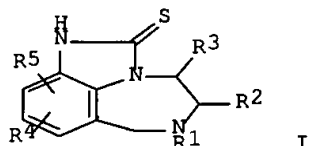
Absolute stereochemistry.



L4 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 1991:62128 CAPLUS
 DN 114:62128
 TI Preparation of antiviral tetrahydroimidazo [1,4] benzodiazepin-2-thiones
 IN Kukla, Michael Joseph; Breslin, Henry Joseph; Raeymaekers, Alfons Herman
 Margaretha; Van Gelder, Josephus Ludovicus; Janssen, Paul Adriaan
 PA Janssen Pharmaceutica N. V., Belg.
 SO Eur. Pat. Appl., 30 pp.
 CODEN: EPXXDW
 DT Patent
 LA English
 FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	EP 384522	A1	19900829	EP 1990-200348	19900216
	EP 384522	B1	19930113		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL				
	IL 93136	A1	19950124	IL 1990-93136	19900123
	AT 84534	E	19930115	AT 1990-200348	19900216
	ES 2046671	T3	19940201	ES 1990-200348	19900216
	CA 2010639	AA	19900823	CA 1990-2010639	19900222
	CA 2010639	C	20010417		
	NO 9000848	A	19900824	NO 1990-848	19900222
	NO 173503	B	19930913		
	NO 173503	C	19931222		
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	AU 617926	B2	19911205		
	JP 02270876	A2	19901105	JP 1990-39883	19900222
	JP 2588624	B2	19970305		
	HU 54158	A2	19910128	HU 1990-896	19900222
	HU 204831	B	19920228		
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	ZA 9001366	A	19911030	ZA 1990-1366	19900222
	CS 275171	B2	19920219	CS 1990-854	19900222
	HU 60742	A2	19921028	HU 1991-3076	19900222
	HU 207322	B	19930329		
	PL 163722	B1	19940429	PL 1990-283921	19900222
	FI 92830	B	19940930	FI 1990-897	19900222
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	CN 1045105	A	19900905	CN 1990-100881	19900223
	CN 1029848	B	19950927		
	US 5270464	A	19931214	US 1993-42858	19930405
	US 5371079	A	19941206	US 1993-132030	19931005
	US 6201119	B1	20010313	US 1994-304951	19941017
PRAI	GB 1989-4108	A	19890223		
	GB 1989-20354	A	19890908		
	US 1989-406626	A	19890913		
	GB 1988-6449	A	19880318		
	US 1989-323585	B2	19890314		
	US 1989-406625	B2	19890913		
	US 1990-476926	B2	19900208		
	EP 1990-200348	A	19900216		
	HU 1990-896	A3	19900222		
	US 1990-549349	B2	19900706		
	US 1990-549777	B2	19900709		
	US 1990-583533	B2	19900917		

US 1991-671238 B1 19910319
 US 1993-42858 A3 19930405
 US 1993-132030 A3 19931005
 OS MARPAT 114:62128
 GI



AB The title compds. [I; R1 = alkyl, alkenyl, alkynyl, cycloalkyl, arylalkyl, cycloalkylalkyl; R2, R3 = H, alkyl; R4, R5 = H, alkyl, halo, cyano, NO2, CF3, OH, alkoxy, amino], were prepd. Thus, a mixt. of 6-chloro-2H-3,1-benzoxazine-2,4(1H)dione and alanine Me ester hydrochloride was refluxed 10 h to give 52-5% S-7-chloro-3,4-dihydro-3-methyl-1H-1,4-benzodiazepine-2,5-dione. The latter was treated with

HNO3 at 0.degree. to give the 9-nitro compd., which was converted to S-2,9-dichloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo[4,5,6-jk]benzodiazepine, which was refluxed with thiourea in EtOH to give I (R1 = CH2CH:CMe2, R2 = Me, R3 = R4 = H, R5 = 9-Cl) (II).

II had an ED50 of 0.0005 .mu.g/mL for inhibition of HIV-1 cytopathic effect on MT-4 cells.

IT **126234-17-1P 126262-73-5P 131645-75-5P 131645-84-6P**

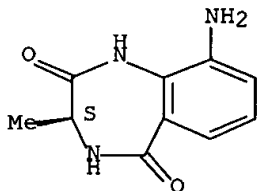
RL: SPN (Synthetic preparation); PREP (Preparation) (prepn. of, as virucide intermediate)

RN 126234-17-1 CAPLUS

CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)-(9CI)

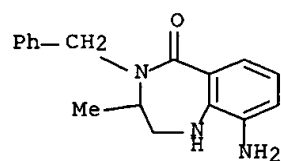
(CA INDEX NAME)

Absolute stereochemistry.



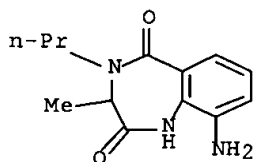
RN 126262-73-5 CAPLUS

CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro-3-methyl-4-(phenylmethyl)- (9CI) (CA INDEX NAME)



RN 131645-75-5 CAPLUS

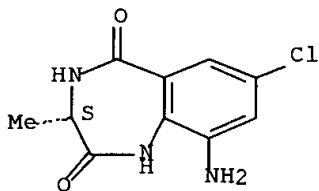
CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-4-propyl-
(9CI) (CA INDEX NAME)



RN 131645-84-6 CAPLUS

CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-7-chloro-3,4-dihydro-3-methyl-,
(S)- (9CI) (CA INDEX NAME)

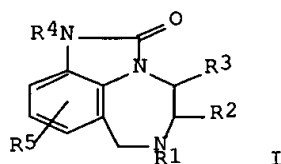
Absolute stereochemistry.



L4 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2003 ACS on STN
 AN 1990:179038 CAPLUS
 DN 112:179038
 TI Preparation and formulation of antiviral
 tetrahydroimidazo[1,4]benzodiazep
 in-2-ones
 IN Raeymaekers, Alfons H. M.; Van Gelder, Josephus L. H.; Kukla, Michael
 J.;
 Breslin, Henry J.; Janssen, Paul A. J.
 PA Janssen Pharmaceutica N. V., Belg.
 SO Eur. Pat. Appl., 21 pp.
 CODEN: EPXXDW
 DT Patent
 LA English
 FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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PI	EP 336466	A1	19891011	EP 1989-200575	19890308
	EP 336466	B1	19921230		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	AT 84035	E	19930115	AT 1989-200575	19890308
	ES 2053946	T3	19940801	ES 1989-200575	19890308
	AU 8931310	A1	19890921	AU 1989-31310	19890314
	AU 617435	B2	19911128		
	JP 01275582	A2	19891106	JP 1989-59859	19890314
	HU 52099	A2	19900628	HU 1989-1240	19890316
	HU 203757	B	19910930		
	CA 1310964	A1	19921201	CA 1989-593935	19890316
	DK 8901309	A	19890919	DK 1989-1309	19890317
	FI 8901279	A	19890919	FI 1989-1279	19890317
	FI 89800	B	19930813		
	FI 89800	C	19931125		
	NO 8901176	A	19890919	NO 1989-1176	19890317
	NO 167737	B	19910826		
	NO 167737	C	19911204		
	ZA 8902062	A	19901128	ZA 1989-2062	19890317
	SU 1748647	A3	19920715	SU 1989-4613664	19890317
	CN 1036957	A	19891108	CN 1989-101474	19890318
	CN 1031058	B	19960221		
	NO 9101970	A	19890919	NO 1991-1970	19910522
	NO 179369	B	19960617		
	NO 179369	C	19960925		
	AU 9183602	A1	19911107	AU 1991-83602	19910902
	AU 630575	B2	19921029		
	US 5371079	A	19941206	US 1993-132030	19931005
	US 6201119	B1	20010313	US 1994-304951	19941017
PRAI	GB 1988-6449	A	19880318		
	GB 1989-4108	A	19890223		
	EP 1989-200575	A	19890308		
	US 1989-323585	B2	19890314		
	NO 1989-1176	A1	19890317		
	GB 1989-20354	A	19890908		
	US 1989-406625	B2	19890913		
	US 1989-406626	B2	19890913		
	US 1990-476926	B2	19900208		
	US 1990-549349	B2	19900706		
	US 1990-549777	B2	19900709		

US 1990-583533 B2 19900917
 US 1991-671238 B1 19910319
 US 1993-42858 A3 19930405
 US 1993-132030 A3 19931005
 OS MARPAT 112:179038
 GI



AB Title compds. I [R1 = H, C1-8 alkyl, C3-6 alkenyl, C3-6 alkynyl, C1-6 alkylcarbonyl, C3-6 cycloalkyl, substituted C1-6 alkyl; R2 = H, C1-6 alkyl, C3-6 alkenyl; R3 = H, C1-6 alkyl; R4 = H, (un)substituted C1-6 alkyl, C1-6 alkoxy carbonyl, C1-6 alkylcarbonyls, C3-6 alkenyl, C3-6 cycloalkyl, C5-6 cycloalkenyl; R5 = H, C1-6 alkyl, halo, (un)substituted Ph] useful as antiviral agents (no data) are prepd. 9-Amino-2,3,4,5-tetrahydro-3-methyl-4-(phenylmethyl)-1H-benzodiazepin-5-one (prepn. given)

and urea were heated to 210-220.degree., the reaction mixt. boiled with HCl, alkalized with NH4OH to give 11.5% I (R1 = PhCH2; R2 = Me; R3-R5 = H).

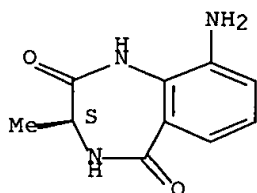
IT **126234-17-1P 126262-73-5P**

RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of, as intermediate for tetrahydroimidazobenzodiazepinone virucides)

RN 126234-17-1 CAPLUS

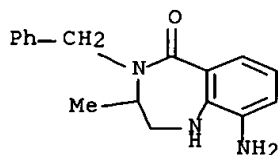
CN 1H-1,4-Benzodiazepine-2,5-dione, 9-amino-3,4-dihydro-3-methyl-, (S)-
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.

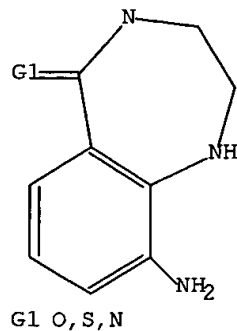


RN 126262-73-5 CAPLUS

CN 5H-1,4-Benzodiazepin-5-one, 9-amino-1,2,3,4-tetrahydro-3-methyl-4-(phenylmethyl)- (9CI) (CA INDEX NAME)



=> d l1; d his; log y
 L1 HAS NO ANSWERS
 L1 STR



Structure attributes must be viewed using STN Express query preparation.

(FILE 'HOME' ENTERED AT 16:40:12 ON 28 OCT 2003)

FILE 'REGISTRY' ENTERED AT 16:40:20 ON 28 OCT 2003

L1 STRUCTURE UPLOADED
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 L3 10 S L1 FUL

FILE 'CAPLUS' ENTERED AT 16:40:41 ON 28 OCT 2003

L4 12 S L3

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
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FULL ESTIMATED COST	54.85	203.21
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-7.81	-7.81

STN INTERNATIONAL LOGOFF AT 16:41:14 ON 28 OCT 2003